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13. ABSTRACT (Maximum 200 Words)

The purpose of this proposal was to develop a consortium of community physicians committed to study novel approaches to the treatment and prevention of breast cancer, provide them with a clinical trials infrastructure linked to an academic center with expertise in basic research and the design and regulation of clinical investigation and to form partnerships with the pharmaceutical industry to facilitate the rapid translation of novel therapeutic approaches to breast cancer. At the time of our most recent annual progress report, we had succeeded in opening additional research sites aimed at increasing participation by patients from underserved populations, and initiating new, investigator-initiated clinical trials. Over the last year of support, the clinical trials network continued to expand and additional breast cancer clinical trials were initiated. Due to a variety of challenges being faced at most academic institutions, over the last two years accrual to clinical trials of patients with cancers other than breast cancer within the UCLA-CORN has decreased. Due to the enhanced support provided through this proposal, we were able to sustain our annual growth in accrual to breast cancer studies.

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INTRODUCTION

Breast cancer is a common and devastating disease. Recent advances in molecular and cell biology have suggested novel, rational approaches to the treatment or prevention of this disease, but the rapid translation of these observations to clinical trials and to practice is hampered by the organization of cancer care in the United States. The basic science observations are often made in academic medical centers, which have neither the patient base nor the capacity to manufacture therapeutic reagents requisite to carrying out a clinical trial. Community-based oncology practices have the patient population, but do not have the needed basic science capacity, biostatistics and clinical trials monitoring infrastructure or therapeutic reagents. The purpose of this proposal was to build a partnership between community physicians and an academic medical center, focused specifically on new approaches to the treatment and prevention of breast cancer, and capable of engaging the collaboration of the pharmaceutical industry in this translational research effort. The program built upon an existing collaboration between community oncologists and UCLA's Jonsson Comprehensive Cancer Center, providing increased ability to focus specifically on breast cancer and expanding access to women from underserved populations. The ultimate goal was to provide an infrastructure for the rapid implementation and successful execution of high quality clinical trials of novel approaches with the promise to increase the survival or decrease the incidence of breast cancer.

BODY

Our initial approved statement of work articulated the following six tasks:

Task 1: Recruitment, training and deployment of three research coordinators (research nurses) and three data managers.
Task 2: Establishment of the community physician network that will participate in the consortium.
Task 3: Initiation of the UCLA-Community Breast Cancer Collaborative Clinical Translational Research Program (UCLA-CBCCCTRP)
Task 4: Initiation of at least five initial breast cancer clinical studies, with accrual of approximately 200 subjects.
Task 5: Ongoing review and selection of additional clinical trials.
Task 6: Ongoing evaluation of the effectiveness of the UCLA-CBCCCTRP

Final Accomplishments Regarding Task 1: Within three months of receipt of this award, we had hired three research coordinators and data managers. These individuals underwent extensive training in research and regulatory methodology, and since the completion of their training in 2001 have been working within the Network on breast cancer clinical trials identified by the Steering Committee as sufficiently meritorious to warrant program support. For the first six months of their work, they were proctored by experienced Cancer Center personnel. The UCLA-CBCCCTRP has supported these individuals continuously throughout the funding period of this grant and they have remained engaged in implementing breast cancer clinical trials. This task was completed in accordance with the timeline in our original approved Statement of Work.

Final Accomplishments Regarding Task 2: As soon as the dedicated research personnel were trained and working, the UCLA-CBCCCTRP began to function, embedded within the existing Network. The presence of these individuals permitted us to expand the number of collaborating practices, recruited specifically to enhance accrual to breast cancer clinical trials. Task 2 was completed in accordance with the timeline in our original approved Statement of Work.

YEAR	M.D.'S	PRACTICES
2001	61	33
2002	71	71
2003	96	49
2004	142	64

Final Accomplishments Regarding Task 3: When the dedicated research personnel supported through this proposal began to work in 2001, the UCLA-CBCCCTRP was initiated. Throughout the funding period, the UCLA-CBCCCTRP continued to thrive and we were able to continually expand the number of participating physicians and practices (see above) and, until recently, the number of patients accrued (see below). This task was completed in accordance with the timeline in our original approved Statement of Work. The decrease in accrual in 2004 corresponded with a shift in the UCLA-CBCCCTRP activities away from larger randomized trials to a focus on smaller, investigator-initiated trials. At least two of these recent studies are expected to lead to large randomized trials, and the number of breast cancer patients accrued in 2005 is expected to rise.

Final Accomplishments Regarding Task 4: The accrual of patients to breast cancer trials through the UCLA-CBCCCTRP is shown in table form below. Over the time period of support, we have exceeded our accrual projections to breast cancer clinical trials. We have supported the implementation of 13 breast cancer clinical trials, a complete listing of which follows the accrual graph. As noted above, accrual to trials in 2005 will be closer to the 2002/2003 levels as the larger trials open.

2001	2002	2003	2004
242	263	190	123

TITLE	OPEN	CLOSED
A Multicenter Phase III Randomized Trial Comparing Docetaxel in Combination with Doxorubicin and Cyclophosphamide (TAC) to 5-Fluorouracil in Combination with Doxorubicin and Cyclosphosphamide (FAC) as First Line Chemotherapy for Metastatic Breast Cancer	1/21/1998	8/10/2000
A Multicenter Phase III Randomized Trial Comparing Docetaxel (Taxotere) and Trastuzumab (Herceptin) with Docetaxel (Taxotere) Platinum Salt (Cisplatin or Carboplatin) and Trastuzumab (Herceptin) as First Line Chemotherapy for Patients	1/30/2002	2/20/2004

with Advanced Brea		
An Open-Label, Multicenter, Single Arm Phase II Study of Oral GW572016 as Single Agent Therapy in Subjects with Advanced or Metastatic Breast Cancer Who Have Progressed While Receiving Herceptin Containing Regimens.	10/25/2002	12/13/2004
A Multicenter Phase II Evaluation of Targretin® (bexarotene) Capsules in Patients with Advanced Breast Cancer (Protocol L1069-34)	10/27/1998	11/08/2000
Pilot Phase II Study of Taxotere (Docetaxel), Carboplatin and Herceptin (T/C/H) in the Treatment of Metastatic Breast Cancer (RPR TCH 11122 Breast)	10/06/1999	12/11/2000
A Multi-Center Phase III Randomized, Controlled Study of THERATOPE Vaccine for Metastatic Breast Cancer (Theratope 104 Breast)	11/11/1998	03/30/2001
A Blinded, Randomized, Multicenter Study to Evaluate Single Administration Filgrastim-SD/01 per Cycle Versus Daily Filgrastim as an Adjunct to Chemotherapy in Subjects with High-Risk Stage II or Stage III/IV Breast Cancer	12/03/1999	04/07/2000
A Multicenter, Open Label, Phase III, Randomized, Active-Controlled Trial Evaluating the Efficacy, Safety, and Pharmacokinetics of rhuMAb VEGF (BEVACIZUMAB), in Combination with Capecitabine Chemotherapy, in Subjects with Previously Treated Metastatic B	02/15/2001	03/29/2002
Phase III A Multicenter Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC>T) with Doxorubicin and Cyclophosphamide Followed by Docetaxel and Trastuzumab (AC>TH) and with Docetaxel, Platinum Salt and Trasuzumab (TCH)	04/30/2001	01/21/2004
Phase III Multicenter Randomized Breast Cancer Trial Comparing Docetaxel in Combination with Doxorubicin and Cyclophosphamide (TAC) verses Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC>T) as Adjuvant Treatment of Operable Breast Cancer her2	05/03/2001	01/07/2003
An Open-Label, Multicenter, Single Arm Phase II Study of Oral GW572016 as Single Agent Therapy in Subjects with Advanced or Metastatic Breast Cancer Who Have Progressed While Receiving Herceptin Containing Regimens (EGF 20008)	07/21/2003	08/13/2004
A Phase II, Multicenter, Open-Label Clinical Trial to Evaluate the Efficacy and Safety of OSI-774 in Patients with Advanced or Metastatic Breast Cancer and Disease Progression During or Following Chemotherapy.	07/06/2001	02/08/2002

Phase III Comparative Study of Herceptin(TM) and Taxol(R) With and Without Carboplatin in HER2-Positive Patients With Advanced Breast Cancer. (Herceptin 98-012)	09/03/1998	05/22/2002

Final Accomplishments Regarding Task 5: The UCLA-CBCCCTRP Steering Committee began meeting in 2001, and continued to meet regularly throughout the support period. The committee selected breast cancer trial for UCLA-CBCCCTRP based upon their assessment of the trial's linkage to a novel basic science hypothesis and/or potential to succeed in improving the outcome for women with breast cancer. All trials that received UCLA-CBCCCTRP support were vetted through this process and approved by the committee. In addition, the committee also reviewed all proposed new physician members of the UCLA-CBCCTRP and assessed their commitment to clinical research focused on the breast cancer problem and their potential for significant accrual to studies. All new members added from 2001 through 2004 were approved by the steering committee. This task was completed in accordance with the timeline in our original approved Statement of Work.

Final Accomplishments Regarding Task 6: The UCLA-CBCCCTRP Steering Committee met twice annually to review implementation of and accrual to breast cancer clinical trials in the Network. The committee consistently found that the program was successfully meting its objectives. This task was completed in accordance with the timeline in our original approved Statement of Work.

KEY RESEARCH ACCOMPLISHMENTS

- A significant increase in the number of community physicians participating in breast cancer clinical trials
- A significant increase in the number of patients enrolled on investigator-initiated breast cancer clinical trials
- Successful completion of several clinical trials exploring novel strategies for the prevention and treatment of breast cancer

REPORTABLE OUTCOMES

Publications:

1. Finn RS, Wilson CA, Sanders J, Cook A, Olson T, Glaspy P, Tchekmedjian N, Pegram MD, Britten C, Slamon DJ. Targeting the epidermal growth factor receptor and HER-2 with OSI-774 and trastuzumab, respectively, in HER-2 overexpressing human breast cancer cell lines results in a therapeutic advantage in vitro. *Proc Am Soc Clin Oncol* 22: (A940), 2003.

2. Britten CD, Pegram M, Rosen P, Finn RS, Wax A, Bosserman LD, Gordon L, Lin LS, Mass R, Slamon DJ. Targeting ErbB Receptor Interactions: A Phase I Trial of Trastuzumab and Erlotinib in Metastatic HER2+ Breast Cancer. *Proc Am Soc Clin Oncol* 23: (A3045), 2004.

3. Pietras, R.J. (2003). Interactions between estrogen and growth factor receptors in human breast cancers and the tumor-associated vasculature. The Breast Journal 9: 361-373.

4. Pegram MD, Konecny GE, O'Callaghan CO, Beryt M, Pietras RJ and Slamon DJ (2004). Rational combinations of Trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer. J. Natl. Cancer Inst. (in press).

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9. Pietras RJ, Marquez D, Chen HW, Ayala R, Ramos L and Slamon DJ (2003). Improved antitumor therapy with Herceptin and Faslodex for dual targeting of HER-2 and estrogen receptor signaling pathways in human breast cancers with overexpression of HER-2/neu gene. Breast Cancer Res. Treatment 82, Suppl. 1: 12-13.

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11. Pio BS, Park CK, Pietras RJ, Satyamurthy N, Pegram M, Czernin J, Phelps ME and Silverman D (2004). Five minutes of imaging with [F-18]fluoro-L-thymidine (FLT) predicts long-term post-therapy response in breast cancer patients. Proc. Soc. Nucl. Med. (in press).

12. Miguel Martin, M.D., Tadeusz Pienkowski, M.D., John Mackey, M.D., Marek Pawlicki, M.D., Jean-Paul Guastalla, M.D., Charles Weaver, M.D., Eva Tomiak, M.D., Taher Al-Tweigeri, M.D., Linnea Chap, M.D., Eva Juhos, M.D., Raymond Guevin, M.D., Anthony Howell, M.D., Tommy Fornander, M.D., John Hainsworth, M.D., Robert Coleman, M.D., Jeferson Vinholes, M.D., Manuel Modiano, M.D., Tamas Pinter, M.D., Shou C. Tang, M.D., Bruce Colwell, M.D., Catherine Prady, M.D., Louise Provencher, M.D., David Walde, M.D., Alvaro Rodriguez-Lescure, M.D., Judith Hugh, M.D., Camille Loret, Ph.D., Matthieu Rupin, M.Sc., Sandra Blitz, M.Sc., Philip Jacobs, Ph.D., Michael Murawsky, M.Sc., Alessandro Riva, M.D., Charles Vogel, M.D. on behalf of the BCIRG 001 Investigators: Adjuvant docetacel plus doxorubicin and cyclophosphamide in breast cancer. New England Journal of Medicine (in press)

Presentations:

1. "Interactions between Type I receptor tyrosine kinases and steroid hormone receptors". Presented at First International Congress on Translational Research in Oncology, Dublin, Ireland (2001).

2. "Monoclonal antibodies for antitumor therapy". Presented at Immunobiology of Cancer Seminar (MI 262A), UCLA (4/2002).

3. "Steroid and growth factor receptors in breast cancer : cross-talk and clinical implications". Presented at Second International Congress on Translational Research in Oncology, Anaheim, CA (2002).

4. "Exploiting synergy between platinum and Trastuzamab in breast cancer: BCIRG and UCLA experiences". Presented at Lynn Sage Breast Cancer Symposium, Northwestern Comprehensive Cancer Center, Chicago, Illinois (2002).

5. "Clinical exploitation of interactions between estrogen and HER-2 receptors in human breast cancer ". Presented at 8th Annual Multidisciplinary Symposium on Breast Disease, A Program of the University of Florida Health Science Center and the Susan G. Komen Breast Cancer Foundation, Amelia Island, Florida (2003).

6. "Estrogen and HER-2 receptor interactions in human breast cancer". Presented at *Symposium on Steroid Hormone Action* at American Society for Cell Biology Annual Meeting, San Francisco, CA (2003).

7. "Interactions of estrogen and HER-2 receptors in human breast cancer". Presented at FASEB Summer Research Conference on Steroid Hormone Receptors, Omni Resort, Tucson, Arizona (2004).

8. "Mechanisms of endocrine resistance in human breast cancer therapy". Presented at "*Meet the Professor*"session at the 2004 American Society for Clinical Oncology (ASCO) Annual Meeting, New Orleans (2004).

9. "Interactions between steroid and peptide hormone signaling pathways for growth: Clinical implications". Fourth International Symposium on Translational Research in Oncology, Dublin, Ireland (2004).

10. "Dual therapy with Faslodex and Herceptin in human breast cancer". Presented at Breast Cancer Summit, Montreaux, Switzerland (2004).

11. "Targeting estrogen and growth factor receptors for breast cancer therapy". Presented at Genentech Symposium, Dana Point (2004).

CONCLUSIONS

Our experience with the UCLA-CBCCCTRP had two very important outcomes. First, as demonstrated above, we were successful in increasing accrual to breast cancer clinical trials and

in executing several very important translational studies that would not otherwise have been possible without the support provided through this grant. Equally importantly, our work provides a model applicable to other institutions for the development of an infrastructure to facilitate more rapid translation of scientific advances into clinical trials through productive engagement of the community. We found that many, but not all, community-based oncologists are willing and able to participate in collaborative research efforts in breast cancer, provided that sufficient infrastructure exists to insure that the work will not tap already strained office staff and resources. We found that the major obstacle to success is the level of commitment of individual physicians, which is often difficult to accurately assess initially. Ongoing evaluation of the commitment of and accrual by individual physicians, with replacement of individuals whose performance does not reflect sufficient commitment was an important part of our success. We recommend that efforts to establish similar research networks incorporate a robust ongoing evaluation function to insure that the resources invested yield maximum benefit in terms of accrual and knowledge gained.

REFERENCES

See Reportable Outcomes